

WHAT IS CLAIMED IS:

1. A method for producing a biomolecule of interest that is not secreted by the host cell, comprising the steps of
 - a) cultivating host cells to produce the biomolecule of interest and optionally harvesting and resuspending the cells,
 - b) disintegrating the cells by alkaline lysis,
 - c) precipitating the cell debris and impurities by neutralizing the lysate,
 - d) separating the lysate from the precipitate obtained in step c),
 - e) purifying the biomolecule of interest,wherein in step d) the mixture comprising the precipitate and the lysate is allowed to gently flow downward through a clarification reactor that is partially filled, in its lower part, with retention material, whereby the precipitate is retained on top of and within the layer of retention material and the cleared lysate leaves the reactor through the bottom of the reactor.
2. The method of claim 1, wherein the lysate of step d) contains the biomolecule of interest.
3. The method of claim 1, wherein the retention layer in the reactor of step d) is composed of a particulate material.
4. The method of claim 3, wherein the retention layer consists of glass beads.
5. The method of claim 1, wherein the retention layer in the reactor of step d) is composed of rigid retention material.

6. The method of claim 5, wherein the retention material comprises sinter plates.

7. The method of claim 1, wherein in step d) increasing pressure is applied to the mixture from the top of the clarification reactor thereby accelerating the process and ensuring a constant outflow of the lysate.

8. The method of claim 7, wherein pressure is increased by applying pressurized air.

9. The method of claim 1, wherein one or more wash steps are inserted between steps d) and e).

10. The method of claim 1, wherein in step b) a cell suspension obtained in a) and an alkaline lysis solution are allowed to flow through a lysis reactor that is filled with particulate material, thereby contacting and gently mixing the flow of the cell suspension with the flow of the alkaline lysis solution.

11. The method of claim 10, wherein the flow of the cell suspension and the flow of the alkaline lysis solution are combined, without further mixing, before entering the lysis reactor, thus forming a single flow that is thoroughly and gently mixed when flowing through the particulate material in the lysis reactor.

12. The method of claim 10, wherein the cell suspension and the lysis solution are introduced into the lysis reactor in the form of two independent flows.

13. The method of claim 12, wherein said two flows are introduced through inlets that are situated close to each other.

14. The method of claim 11 or 12, wherein said two flows are transported at a defined ratio of flow rates, thereby ensuring a constant ratio of cell suspension and lysis solution volumes.

15. The method of claim 1, wherein in step c) the lysed cell solution obtained in step b) is mixed with the neutralizing solution in a continuous mode.

16. The method of claim 15, wherein the lysed cell solution and the neutralizing solution are combined at a constant ratio of flow rates, thereby ensuring mixing, neutralizing and precipitating during transportation between step b) and step d).

17. The method of claim 1, wherein a concentration and/or a conditioning step is inserted between step d) and step e).

18. The method of claim 17, wherein said concentration step takes place before said conditioning step.

19. The method of claim 1, wherein said biomolecule of interest is a polynucleotide.

20. The method of claim 17, wherein the polynucleotide is plasmid DNA.

21. The method of claim 1, wherein at least one steps selected from steps b) to e), including the optional conditioning step, is operated in a continuous and automated mode.

22. The method of claim 21, wherein at least a combination of two steps selected from steps b) to e), including the optional conditioning step, is operated in a continuous and automated mode by connecting the two or more individual steps.

23. The method of claim 21 or 22 wherein, in addition, step a) is operated in a continuous mode by being connected to step b).

24. The method of claim 1, wherein the cell mass obtained in step a) is cryo-pelleted.

25. A reactor for carrying out step d) in the method of claim 1, comprising

- a) a retention layer in its lower part,
- b) an inlet at a position above the retention layer,
- c) an outlet underneath the retention layer, and
- d) one or more distribution means that reach to the surface of the retention layer and evenly and gently distribute a mixture of precipitate and lysate as obtained upon alkaline lysis and neutralization into the reactor.

26. The reactor of claim 25, wherein a single distribution means is located vertically in the center of the reactor.

27. The reactor of claim 26, wherein said distribution means is connected with a supply means that introduces said mixture through the inlet.

28. The reactor of claim 26, wherein said distribution means is an extension of a supply means that delivers said mixture through the inlet.

29. The reactor of any one of claims 25 to 28, wherein the distribution means is a tube having apertures.

30. The reactor of claim 29, wherein said tube carries a rod in its center.

31. The reactor of any one of claims 25 to 28, wherein the distribution means is a coil having apertures.

32. The reactor of claim 29, wherein the apertures are slots or perforations.

33. The reactor of claims 25, wherein said distribution means is a chute.

34. The reactor of claim 25, comprising in addition means for supply of compressed gas.

35. A lysis reactor for carrying out the method of claim 9, comprising a flow-through container that is filled with a particulate material.

36. The reactor of claim 35, wherein the container is in the form of a cylinder.

37. The reactor of claim 35 or 36, wherein the particulate material comprises glass beads.

38. A neutralization reactor for carrying out the method of claim 14, comprising a connector means for combining the flows of the lysed cell solution and the neutralization solution, and a tubing system for homogenous mixing and reacting the lysed cell solution with the neutralization solution.

39. The reactor of claim 38, wherein the tubing is in the form of a coil.